14. A process according to claim 13, wherein said hydrolysate is characterized by the following Molecular Weight Profile (HPLC):

Range (Daltons)	Soluble Peptides
> 5000	50 - 55%
2000 – 5000	15 - 20%
< 2000	30 – 35.

15. A process according to claim 14, wherein said reaction is stopped when the degree of hydrolysis is within the range of from 5.5 to 6.5%.

REMARKS

Reconsideration and allowance of original and amended claims 1-3, 5 and 6 and new claims 7-15, all of the claims pending in the application, are respectfully requested in view of the above amendments, these remarks and the accompanying Declaration of Anand Rao, Ph.D. Claims 1 and 6, the two independent claims originally in the application, have been amended. Claims 7-15 have been added, and claim 4 has been canceled.

It will be recalled that the invention relates to inhibiting angiotensin-converting enzyme (ACE) for treatment of mammals with specific hydrolysates obtained by the enzymatic conversion of whey proteins.

The description notes that hypertension is a significant medical and social problem. In deed, it has been reported to be the most important cause of human deaths in industrialized countries. (See, for example, Laragh, J. H., 1979, L'hypertension. *Recherche*, 105 (10): 1068-1076.) Nearly 30% of the fatalities among adults would result from hypertension or from its renal, coronary or neurological complications. The elucidation of the physiological mechanisms responsible for hypertension has lead to the

introduction of several pharmaceuticals for the treatment of hypertension and/or its symptoms, which include increased heart rate and increased blood pressure.

The invention identifies additional materials capable of treating hypertension or its symptoms, especially materials that can be easily employed as part of a simple regimen, such as including them in food items. It will be seen from the following description that, while the inclusion of various antihypertension materials have been suggested for use in foods, the procedures utilized to produce them are so inefficient as to make this fully impractical to one skilled in the art. The products of the inventive procedures, are highly effective as shown in the accompanying Declaration of Anand Rao, Ph.D.

Claims 1-6 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as their invention. This rejection is respectfully traversed in view of the amended claims as presented herein. The noted formal matters have all been addressed, and the Examiner's suggestions adopted for all but the "regimen" limitation, which has been corrected in the manner noted above. If any further formal matters remain, the Examiner is requested to call the undersigned for further discussion.

In addition to the amendments noted above, the claims have been amended to highlight several distinguishing features. First, original claims 1 and 6, and new claim 12, has been limited to the source of enzyme as comprising *trypsin*. These claims are further limited to clarify the fact that the reaction is stopped and the *hydrolysate* is dried, as set forth in the Description in the paragraph bridging pages 8 and 9. Also, claims 8, 12 and 13 include the limitation that the degree of hydrolysis is within the range of from 5.5 to 20.5%, a composite range of the three samples reviewed in the noted paragraph. Claim 9 and 15 include the degree of hydrolysis range for the production of the material identified as AS-601.

In addition to these points, new claims 10 and 13 specify the source of the whey protein as being a whey protein isolate prepared by ion exchange processing and characterized by a protein content of at least 94% and an ash content of less than 3%. This amendment is supported by the last full paragraph on page 4 of the Description.

Also, please note that claim 4 has been canceled as being redundant with the limitations now added to its base claim 1.

Claims 1-6 have been rejected under 35 U.S.C. §102(b) as defining an invention that is anticipated by JP 04082898, cited by applicants. An International Search Report in the PCT application (PCT/US01/14797) claiming this application as a priority document cited three different Japanese patent documents, namely JP 042892400, JP 04282398 and JP06345664, as being of particular relevance (Y) "when taken with one or more other documents". The rejection over JP 04082898 is respectfully traversed in view of the amended claims as presented herein. The other references, including JP 042892400, are distinguished also.

All claims define novel subject matter as amended or newly presented. The references do not teach the specifically claimed materials or processing which provide the path to the achievement of the results set out in the examples and as more fully explained herein and in the Declaration of Dr. Rao. In particular, the claims now call for the enzyme by source and clarify that the hydrolysate can simply be dried after the reaction is stopped as set forth in the paragraph bridging pages 8 and 9 of the Description.

To be clear as to why applicants believe that the subject to a rejection for anticipation is not proper in view of the claims as now presented, applicants point to the above factual distinctions and to the law of anticipation. For a rejection for anticipation to be fully correct, all material elements recited in a claim must be found in one piece of prior art. Here, the Japanese references do not teach the claimed combination of steps including the starting materials and end product. The law of anticipation requires that the

same invention, with all the limitations of the claims, has existed in the prior art. See *Richardson v. Suzuki Motor Co.,* 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920-21 (Fed. Cir. 1989) ("anticipation" requires that the identical invention is described in a single prior art reference). Where the reference does not describe each limitation, the invention is novel and has met at least this condition of patentability.

The present invention is novel. The process calls for whey protein to be hydrolyzed until a hydrolysate is achieved having increased ACE-suppressing activity. The hydrolysate can then be dried for use. It does not require the purification of the hydrolysate and a special isolation procedure to obtain a narrow tripeptide fraction (Leu-Lys-Pro) as called for in JP 04082898 (which did not utilize trypsin). In addition, claims 7 and 12, and 14 identify molecular weight ranges not described in this reference nor likely to be inherent in the production geared to yield a specific tripeptide having a molecular weight of less than 300 Daltons (Leu=131.2 + Lys=146.2 + Pro=115.1). Claims 7, 12 and 14 further highlight the distinctions over the reference by specifying the molecular weight ranges of the products in combination with other distinguishing features. Thus, each of the claims defines a combination of features not specifically disclosed by the reference and a rejection under 35 U.S.C. §102(b) cannot be sustained.

In addition, the claims were rejected under 35 U.S.C. §103(a) as defining an invention obvious from JP 04082898. This rejection is respectfully traversed as to this reference and to the extent of applicability of the references cited in the noted International Search Report in the PCT application. None of the references teach the person skilled in the art that there would be some purpose to be achieved or some objective advanced by modifying any of the prior art procedures in the manner claimed in the present application.

Applicants point out that JP 04082898 is directed to the preparation of a particular purified tripeptide fraction (Leu-Lys-Pro) and obtains it specifically by hydrolyzing whey protein with pepsin followed by Alpaltic Proteinase. Already the process is more complex

than would be desired for making an additive suitable for use in a food. The hydrolysate in then further subjected to centrifuging, drying, rehydrating, purifying and analysis to confirm recovery of the noted tripeptide. There is no recognition that the presently claimed trypsin can or should be used to obtain a hydrolysate of mixed formulation. The process of JP 04082898 provides no general guidance as to the preparation of suitable hydrolysates useful as such. Indeed, the reference always requires specific confirmation of the presence of the noted tripeptide. There is no reason why the person skilled in the art would believe that a process modified to eliminate the analysis and purification could be effective.

The complicated processing of JP 04082898 is obviated by the present invention without diminishing the effectiveness of the resulting product. The description of the process of JP 04082898 reports collecting 1200 μg powder from the initial 5 grams of whey protein starting material. This amounts to a recovery of 0.024%, which is actually in the parts per million range – namely 240 ppm product for each gram of starting material. The tests run in JP 04082898 show the ACE inhibiting IC50 concentration to be 2.2 μM (0.6 mg/ml). The present invention makes it possible, starting with a different enzyme and utilizing different reaction targets – the production of a hydrolysate with ACE inhibiting effect – to utilize a simple recovery technique and yet achieve IC50 values on this same order (*e.g.*, 0.45 mg/ml for AS-601 made from *Bi*PRO® utilizing trypsin). Thus, the results achieved by the present invention are surprising in addition to being produce by novel process.

To further demonstrate the clear differences between the invention and the prior art and to illustrate their unobviousness, applicants submit the accompanying Declaration of Anand Rao, Ph.D. In the Declaration Dr. Rao indicates that he has reviewed JP 04282400, believed to constitute the closest prior art, and has determined several significant factors demonstrating the invention to be unobvious from and a clear improvement over the products and processes of that reference.

Dr. Rao has drawn the following three significant conclusions based upon his comparison of the teachings of JP 04282400 to the subject matter taught and claimed in the present application:

(1) A comparison of the process of JP 04282400 to that of the invention shows the invention to be more practical.

(2) Reported results of animal investigations for the products of JP 04282400 show a product of far less activity than similar tests run utilizing products of the present invention.

(3) Products of JP 04282400 prepared by a procedure modified to provide a fair comparison showed lower effectiveness for ace inhibition than the products of the invention.

The comparison to JP 04282400 is probative because it does relate to closely-related prior art and the prior art is, in fact to be closer than, JP 04082898. On this point, applicants again point out that the process of JP 04082898 does not utilize trypsin. Moreover, it is concerned with directing the hydrolysis and the recovery techniques to obtain a very specific tripeptide. Thus, it is not as close as the JP 0428400 reference, which at least relates to trypsin, although it employs complicated processing and achieves low yields.

Applicants note that the Declaration of Dr. Rao is proper under 37 CFR 1.132 because it compares the claimed subject matter with the closest prior art. As such it is effective to rebut a *prima facie* case of obviousness. *In re* Burckel, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979). The Declaration is proper in that Applicants compare the claimed invention with prior art that is more closely related to the invention than the prior art relied upon by the examiner. *In re* Holladay, 584 F.2d 384, 199 USPQ 516 (CCPA 1978); *Ex parte* Humber, 217 USPQ 265 (Bd. App. 1961) (Claims to a 13-chloro substituted compound were rejected as obvious over nonchlorinated analogs of the claimed compound. Evidence showing unexpected results for the claimed compound as compared with the 9-, 12-, and 14- chloro derivatives of the compound rebutted the *prima*

facie case of obviousness because the compounds compared against were closer to the claimed invention than the prior art relied upon.).

While applicants have not reproduced all of the prior art procedures, it is believed that the comparisons made show that there is no reason to assume that all procedures for obtaining a whey protein hydrolysate will function similarly. Indeed, the procedure of the invention is demonstrated to be superior to one of the principal references cited against the present invention. That such results were achieved is unexpected and, as such, evidence of unobviousness.

Clearly, any case of unobvious based on any of the cited references is *prima facie* only and subject to rebuttal. Evidence of unobvious or unexpected advantageous properties, such as superiority in the property now claimed is sufficient to rebut *prima facie* obviousness. See, *In re* Chupp, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987) (Evidence showing that the claimed herbicidal compound was more effective than the closest prior art compound in controlling quackgrass and yellow nutsedge weeds in corn and soybean crops was sufficient to overcome the rejection under 35 U.S.C. 103, even though the specification indicated the claimed compound was an average performer on crops other than corn and soybean.). See also *Ex parte* Party A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (unexpected superior therapeutic activity of claimed compound against anaerobic bacteria was sufficient to rebut prima facie obviousness even though there was no evidence that the compound was effective against all bacteria).

Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See *In re* Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) and MPEP § 716.02(d) - § 716.02(e). See *In re* Blondel, 499 F.2d 1311, 1317, 182 USPQ 294, 298 (CCPA 1974) and *In re* Fouche, 439 F.2d 1237, 1241-42, 169 USPQ 429, 433 (CCPA 1971), cases where indirect comparative testing was found sufficient to rebut a prima facie case of obviousness.

Moreover, the fact that applicant tested but one of several novel products is still evidence for the claim as drawn. The nonobviousness of a claimed range can be supported by evidence based on unexpected results from testing a narrower range if one of ordinary skill in the art would be able to determine a trend in the exemplified data, which would allow the artisan to reasonably extend the probative value thereof. See, *In re* Kollman, 595 F.2d 48, 201 USPQ 193 (CCPA 1979).

Accordingly, there can be no obvious of subject matter without a clear direction to the person skilled in the art to make the invention as claimed. The portions of the references referred to in the Office Action are of a general nature and do not address the particular improvements claimed herein. Indeed, the invention provides advantages, as set out in the examples, that are of a nature and degree not contemplated by the references.

Applicants have made a significant advance in the art of inhibiting angiotensin-converting enzyme (ACE). The claims clearly and concisely set this invention out in terms that patentably distinguish from the prior art. Accordingly, reconsideration and allowance of all claims are believed in order, and such actions are earnestly solicited.

Respectfully submitted,

Date: March 25, 2002

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Marked-Up Versions of Amended Claims

1. (Amended) A process for preparing an angiotensin-converting enzyme (ACE)-inhibiting [suppressing] composition comprising:

preparing an aqueous solution of whey protein isolate and a proteolytic enzyme, comprising trypsin;

holding said solution under conditions effective for reaction to partially hydrolyze said whey protein isolate to provide a hydrolysate having increased ACE-suppressing activity [in mammals];

stopping the reaction; and

drying [recovering] said hydrolysate [from said solution].

6. (Amended) A treatment regimen for a mammal to [suppress] inhibit angiotensin-converting enzyme (ACE), said regimen comprising:

orally administering to the mammal, a product prepared according to claim 1 in amounts and at intervals effective to suppress ACE-activity.